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704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

Cytokine Profile Following Varnimcabtagene Autoleucel (IMN-003A) in Patients with Relapsed Refractory B Cell Malignancies in the First-in-India Industry Phase-2 Study (IMAGINE)

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Background: Varnimcabtagene autoleucel (Var-cel, IMN-003A) is an autologous CD19 directed CAR-T cell product with a 4-1BB co-stimulatory domain and a non-FMC63 murine single chain variable fragment (A3B1 binder), manufactured in India, tested in the IMAGINE study (CTRI/2022/03/041162), a phase-2 clinical trial for patients (pts) with relapsed and/or refractory B cell malignancies. This abstract evaluates the cytokine profile and its correlation with safety outcomes and CAR-T expansion following var-cel infusion.

Methods: Serum was collected pre-infusion and upto 13 timepoints post infusion as per study schedule for evaluating cytokine levels. Nine cytokines (IFN-g, TNF-α, IL-1β, IL-2, IL-7, IL-8, IL-10, IL-15 and MCP-1) were measured using a multiplexed kit on the Magpix platform. IL-6 level was measured using electrochemiluminescence immunoassay (ECLIA). Safety and adverse event data were collected for analysis along with measuring various cytokine levels in the serum. CAR-T persistence post infusion was monitored using ddPCR.

Results: 24 patients (pts) were infused with var-cel in the IMAGINE study. Var-cel levels in peripheral blood post-infusion were measured at multiple timepoints for all infused pts using ddPCR platform. The var-cel levels peaked (Tmax) at a median of 10 days post infusion (D+10; range: 10 - 28 days) with median Cmax of 125,242 (range 18,256 - 413,968 copies/µg genomic DNA). The median duration of persistence was 56 days with persistent CAR seen in 3 pts at last follow-up.

Adverse events of special interest (AESIs) reported were CRS (Grade [G] 1 62.5%; G3+ 4.2%; overall 66.7%) and ICANS (G1 4.2%; G3+ 0%; overall 4.2%). The median onset of CRS at D+5, 5 days before the median var-cel Tmax of D+10. The median duration for CRS was 3 days. No G3+ ICANS was reported.

Serum IL-6 levels peaked at a median of D+7 post infusion and reached above 40 pg/mL for 13 pts, all of whom experienced CRS. All eight pts with no CRS had peak IL-6 levels below 40 pg/mL. Despite this significant association with CRS ($p<0.001$, Man-Whitney test) and published causation, IL-6 level peaked towards the end of clinical course of CRS manifestation, but usually at or before peak var-cel expansion (Tmax). Interestingly, the increase in IL-6 levels tended to begin early and persist longer for some B-NHL patients compared to B-ALL patients.

Preliminary multiplexed cytokine analysis for evaluated pts (n=6) indicated that IFN-γ, TNF-α, IL-1β, IL-2, IL-7, IL-8 remained within published physiological limits for most patients at all timepoints (except one pt with highest levels at screening). One patient showed mild increase in IFN-γ (peak 50.88 pg/mL) and two pts showed mild increase in IL-8 around D+4 to D+7 (peak 47.71 pg/mL). IL-15 and MCP-1 levels were relatively higher (>2 fold) from D0 to D+7 post infusion, compared to the screening timepoint, consistent with the duration of CRS. Only IL-10, an anti-inflammatory and cytokine synthesis inhibitory factor stood out having a sharp peak (median: 230 pg/mL) for all six patients at D+4 to D+10, consistent with the timeline for end of CRS and before var-cel Tmax. Occasional pt with no clinical CRS also showed IL-10 peak. Updated cytokine profile data shall be presented at the meeting.

Conclusions: This is the first-in-India industry study evaluating cytokine profile at multiple timepoints before and after var-cel infusion and its correlation with clinical CRS. As per published literature, IL-6 levels were significantly associated with clinical

CRS and showed association with peak var-cel expansion. There was a sharp increase in both IL-6 and IL-10 levels in serum post infusion, concurrent with clinical CRS prior to peak var-cel expansion. A further detailed study of cytokine profile following var-cel infusion shall help prognosticate safety outcomes.

Disclosures Dhar: *Immuneel Therapeutics Private Limited:* Current Employment. **Shetty:** *Immuneel Therapeutics Private Limited:* Current Employment. **T.I.:** *Immuneel Therapeutics Private Limited:* Current Employment. **Joseph:** *Immuneel Therapeutics Private Limited:* Current Employment. **Krishnan:** *Immuneel Therapeutics Private Limited:* Current Employment. **Arasu:** *Immuneel Therapeutics Private Limited:* Current Employment. **Elluru:** *Immuneel Therapeutics Private Limited:* Current Employment. **Akheel:** *Immuneel Therapeutics Private Limited:* Current Employment. **Nahar:** *Immuneel Therapeutics Private Limited:* Current Employment. **Gandikota:** *Immuneel Therapeutics Private Limited:* Current Employment. **Kamat:** *Immuneel Therapeutics Private Limited:* Current Employment.

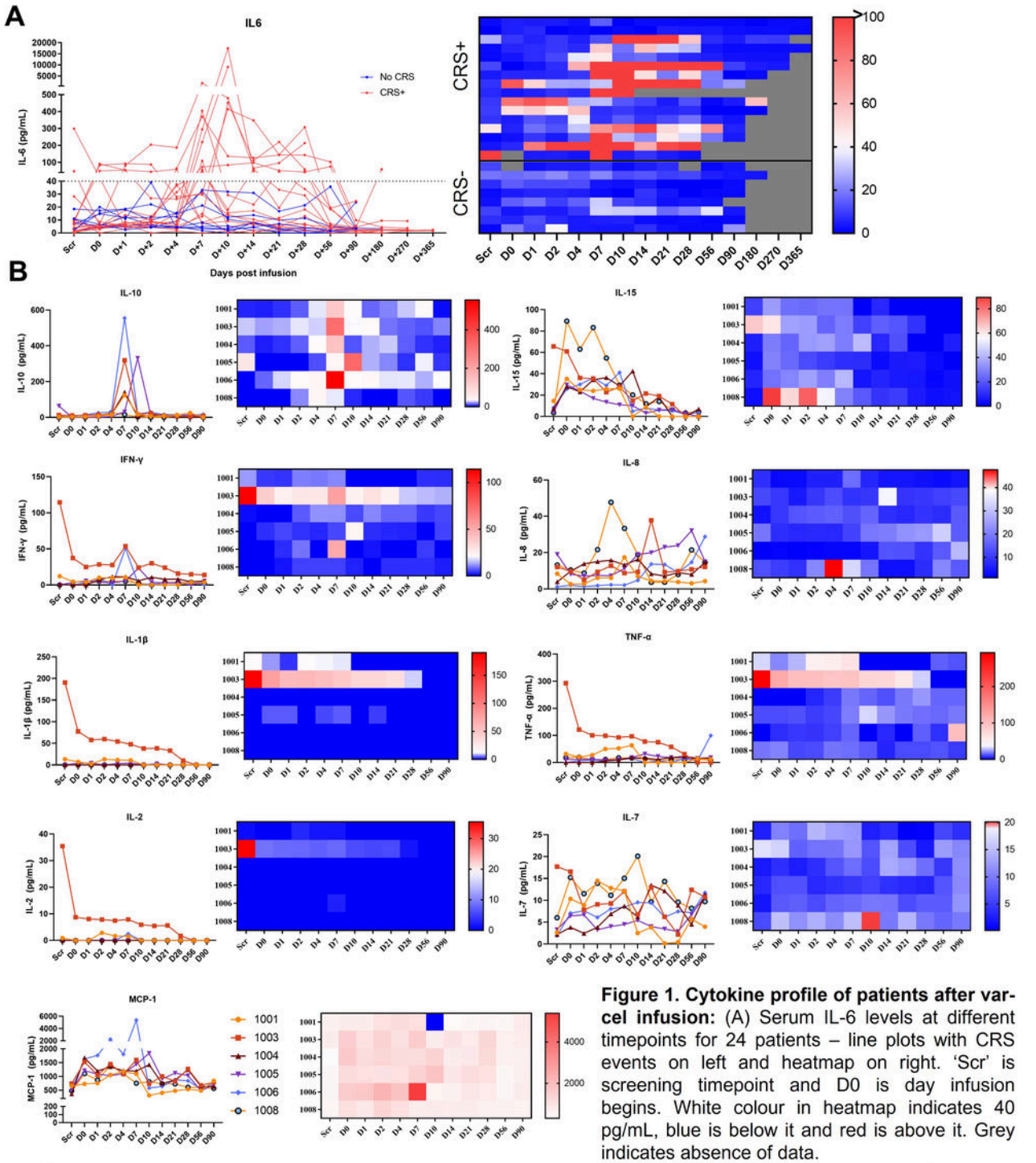

Figure 1. Cytokine profile of patients after varcel infusion: (A) Serum IL-6 levels at different timepoints for 24 patients – line plots with CRS events on left and heatmap on right. 'Scr' is screening timepoint and D0 is day infusion begins. White colour in heatmap indicates 40 pg/mL, blue is below it and red is above it. Grey indicates absence of data.

(B) Line plots and heatmaps depicting levels of nine other cytokines (IFN-γ, TNF-α, IL-1β, IL-2, IL-7, IL-8, IL-10, IL-15 and MCP-1) in 6 patients evaluated at different timepoints, using multiplexed assay. Symbols and colours for the 6 patients are same in all line plots, as shown for MCP-1. Blue-white colour in heatmap indicates published physiological range (healthy subjects) and red is above it.

Figure 1

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